

CHILDHOOD EXPOSURE TO SIMIAN VIRUS 40-CONTAMINATED POLIOVIRUS VACCINE AND RISK OF AIDS-ASSOCIATED NON-HODGKIN'S LYMPHOMA

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Persons with acquired immunodeficiency syndrome (AIDS) have increased risk for non-Hodgkin's lymphoma (NHL). Recent studies have reported the detection of DNA sequences from simian virus 40 (SV40), a macaque polyomavirus that contaminated early poliovirus vaccines, in a large proportion of AIDS-associated NHLs. To examine the association between SV40 exposure and NHL risk, we analyzed data from a U.S. registry-based cohort study of persons with AIDS (1980–96). We calculated NHL incidence in persons born in 1958–61 (exposed to SV40-contaminated poliovirus vaccine as children, $n = 39,468$) and in 1964–67 (born after vaccines were cleared of SV40 and thus unexposed, $n = 17,340$). Among persons with AIDS, NHL incidence was 11.7 per 1,000 person-years in SV40-exposed individuals (616 NHL cases) and 10.1 per 1,000 person-years in SV40-unexposed individuals (230 cases; unadjusted relative risk 1.15, 95% CI 0.99–1.34, $p = 0.06$). Because of differences in cohorts' birth years and the evolving demographics of the AIDS epidemic, SV40-exposed subjects were older at AIDS onset than unexposed subjects (mean age 32.0 vs. 27.2 years, $p < 0.0001$), and the cohorts differed by sex ($p < 0.0001$) and ethnic group ($p < 0.0001$). Since NHL incidence was relatively high among whites ($p < 0.0001$) and homosexual males ($p < 0.0001$) and increased with age ($p = 0.09$), comparisons required adjustments for these factors. After adjustment, SV40 exposure was not associated with NHL incidence (adjusted relative risk 0.97, 95% CI 0.79–1.20, $p = 0.80$). We conclude that childhood exposure to SV40 through receipt of contaminated poliovirus vaccine was not associated with increased risk for AIDS-associated NHL. Our findings do not support a role for SV40 in lymphomagenesis among immunosuppressed persons.

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Key words: Simian virus 40; acquired immunodeficiency syndrome (AIDS); human immunodeficiency virus (HIV); non-Hodgkin's lymphoma; vaccine

Non-Hodgkin's lymphoma (NHL) occurs excessively in persons with acquired immunodeficiency syndrome (AIDS), and its diagnosis in a person with human immunodeficiency virus (HIV) infection is considered AIDS-defining. AIDS-associated NHLs, mostly high-grade B-cell tumors, are thought to arise in the setting of HIV-related destruction of the CD4⁺ T lymphocytes that regulate B-lymphocyte proliferation. Other viruses, including Epstein-Barr virus and Kaposi's sarcoma-associated herpesvirus, may play a role in some cases.^{1–3}

Of interest, Vilchez *et al.*⁴ and Shivapurkar *et al.*⁵ recently reported the detection of DNA from simian virus 40 (SV40), a macaque polyomavirus, in tumor tissues from diverse types of NHL, specifically 50% of NHLs from HIV-uninfected individuals and 33–46% of AIDS-associated NHLs. A link between SV40 and NHL is plausible, since the SV40 genome encodes a protein (T antigen) that inactivates the cellular tumor suppressor proteins p53 and pRb,⁶ and SV40 causes malignancies (including leukemia and lymphoma) in laboratory rodents.^{7–10} Some researchers have identified SV40 DNA sequences in human tumors other than NHL,^{11–15} although these findings have not been confirmed by others.^{16–18}

The source of SV40 DNA sequences in these NHL tissues is uncertain. Infection might have occurred through receipt of poliovirus vaccines during 1955–62, since SV40 was a widespread contaminant of these early vaccines.¹⁹ This contamination occurred before the 1960 discovery of SV40,²⁰ a time when poliovirus vaccines were produced in monkey kidney tissue cultures

harboring SV40 and manufacturing procedures did not wholly inactivate the virus.^{19,21} Tens of millions of people in the United States, mostly children, were exposed to SV40 through large-scale poliovirus vaccination campaigns during these years. After changes in production techniques to eliminate SV40, vaccine lots released in 1963 and after were free of this virus.¹⁹ Among the NHL patients described by Vilchez and Shivapurkar,^{4,5} it is unclear how many had been exposed to SV40-contaminated poliovirus vaccines, although some were born after 1963.

Laboratory studies of tumor tissues do not provide information on NHL risk among SV40-exposed or -infected individuals. To address this question, we studied NHL incidence in a large U.S. cohort of persons with AIDS. We hypothesized that SV40 might be especially likely to cause NHL among this immunosuppressed population. Further, given the high proportion of AIDS-associated NHLs reported to have detectable SV40 DNA,^{4,5} we reasoned that an effect of SV40 exposure on NHL risk should be readily apparent. We thus sought to determine whether persons with AIDS who were born before 1963 (most of whom would have received poliovirus vaccines as young children, when SV40 contamination was prevalent) had a higher risk of NHL than those born subsequently, after poliovirus vaccines were cleared of SV40.

MATERIAL AND METHODS

We used data from the AIDS Cancer Match Registry study. As described previously,²² this study provides data on cancer incidence in persons with AIDS, through linkage of AIDS and cancer registries from 11 U.S. regions (1980–96): the states of Connecticut, Florida, Illinois, Massachusetts, New Jersey and New York, and the metropolitan areas of Atlanta, Los Angeles, San Diego, San Francisco and Seattle. AIDS Cancer Match Registry subjects were those persons with an AIDS diagnosis (as documented in an AIDS registry) in the period covered by the relevant cancer registry. The overall period was 1980–96, but this varied by region.²²

For our present study, we included adults (aged 15 years or more) registered with AIDS, who were born either in 1958–61 (considered SV40-exposed, since most would have received at least 1 dose of poliovirus vaccine potentially contaminated with SV40) or in 1964–67 (considered SV40-unexposed, since they were born after poliovirus vaccines were cleared of SV40).¹⁹ The years 1962–63 were excluded from analysis because this was a transition period in which changed production techniques resulted in a decreasing prevalence of SV40 contamination in administered vaccines.¹⁹ Additional information considered included sex, HIV risk group, ethnic group and geographic area (registry), and age, calendar year and CD4 count at AIDS onset.

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The incidence of NHL (primary outcome) was measured for the 2-year period immediately after AIDS onset (4–27 months post-AIDS onset), based on NHLs recorded in AIDS and cancer registries. We excluded subjects who developed NHL in the AIDS-onset period (0–3 months post-AIDS onset) from these analyses, since NHL is itself an AIDS-defining condition, which artifactually increases NHL incidence in the onset period. We also excluded the period 28–60 months post-AIDS onset from analysis because cancer incidence may be overestimated in this period.²² In secondary analyses, we examined NHL incidence by site (central nervous system, lymph node, other/unknown site) and histologic subtype, classified according to the Working Formulation.²³ AIDS registries specify central nervous system lymphomas as a unique category, so this subtype was identified by information in either AIDS or cancer registries. Nodal lymphomas and separate histologic subtypes were identified through cancer registry data.

Subjects contributed person-time at risk for NHL until the earliest of death, loss to follow-up or 27 months after AIDS onset. We used Poisson regression to compare NHL incidence in subgroups of subjects and to adjust for potential confounding in multivariate analyses.

RESULTS

Our study included 56,808 adults with AIDS: 39,468 SV40-exposed (who were born in 1958–61) and 17,340 SV40-unex-

posed (born 1964–67). These 2 cohorts differed significantly in composition (Table I). Specifically, although the cohorts had the same proportion of homosexual men, the exposed cohort had more nonhomosexual men (25.6% vs. 20.7%) and fewer women (18.8% vs. 23.7%). Also, the exposed cohort had more whites than the unexposed cohort (44.4% vs. 37.8%), with correspondingly reduced proportions from other ethnic groups. As a direct result of the differences in birth years in the 2 cohorts, SV40-exposed subjects were older (mean age at AIDS onset, 32.0 vs. 27.2 years) and developed AIDS earlier (mean year of AIDS onset, 1991.9 vs. 1992.8; $p < 0.0001$) than SV40-unexposed subjects. Registry areas differed between SV40-exposed and -unexposed subjects, most notably with SV40-exposed subjects being more frequently from New York and less frequently from Florida (Table I).

CD4 counts were available for 28,826 subjects (51%). CD4 counts were often not available in the 1980s and did not become systematically collected until 1993, when the definition of AIDS changed to include persons with CD4 counts < 200 cells/mm³. In addition, CD4 counts were not available for New York (14,438 subjects). Excluding pre-1993 and New York subjects, CD4 counts were available for 90% of subjects. Among those with reported values, CD4 counts in SV40-exposed and -unexposed individuals did not differ ($p = 0.18$, Table I).

In the 2-year period after AIDS onset, 846 NHLs were observed in these individuals (incidence 11.2 per 1,000 person-years). NHL

TABLE I—DEMOGRAPHIC CHARACTERISTICS OF 56,808 PERSONS WITH AIDS, BY EXPOSURE TO SV40-CONTAMINATED POLIOVIRUS VACCINE

Characteristic	Exposed ($n = 39,468$)	Unexposed ($n = 17,340$)	p -value
Sex and HIV risk group, n (%)			<0.0001
Male homosexual	21,972 (55.7)	9,640 (55.6)	
Other male	10,095 (25.6)	3,583 (20.7)	
Female	7,401 (18.8)	4,117 (23.7)	
Ethnic group, n (%)			<0.0001
White	17,535 (44.4)	6,547 (37.8)	
Black	13,176 (33.4)	6,375 (36.8)	
Hispanic	8,354 (21.2)	4,197 (24.2)	
Other/unknown	403 (1.0)	221 (1.3)	
Age at AIDS onset, n (%)			<0.0001
15–20	1 (0.0)	68 (0.4)	
21–23	49 (0.1)	881 (5.1)	
24–26	1,026 (2.6)	3,945 (22.8)	
27–29	5,075 (12.9)	9,022 (52.0)	
30–32	12,555 (31.8)	3,410 (19.7)	
33–35	16,339 (41.4)	14 (0.1)	
36–38	4,423 (11.2)	0 (0.0)	
Mean age (SD)	32.0 (2.7)	27.2 (2.2)	
Calendar year of AIDS onset, n (%)			<0.0001
1980–84	144 (0.4)	7 (0.0)	
1985–87	1,683 (4.3)	198 (1.1)	
1988–90	6,902 (17.5)	1,600 (9.2)	
1991–93	14,937 (37.9)	6,051 (34.9)	
1994–96	15,802 (40.0)	9,484 (54.7)	
Mean year (SD)	1991.9 (2.5)	1992.8 (2.1)	
CD4 count, cells/mm ³ , n (%) ¹			0.18
100+	7,580 (40.8)	4,330 (42.4)	
50–99	3,018 (16.2)	1,548 (15.1)	
0–49	8,003 (43.0)	4,347 (42.5)	
Mean CD4 count (SD)	106 (131)	108 (134)	
Registry, n (%)			<0.0001
Atlanta	2,077 (5.3)	1,145 (6.6)	
Connecticut	1,235 (3.1)	519 (3.0)	
Florida	7,491 (19.0)	3,921 (22.6)	
Illinois	2,348 (6.0)	1,180 (6.8)	
Los Angeles	4,630 (11.7)	2,141 (12.4)	
Massachusetts	1,860 (4.7)	770 (4.4)	
New Jersey	4,701 (11.9)	2,028 (11.7)	
New York	10,495 (26.6)	3,843 (22.2)	
San Diego	1,161 (2.9)	578 (3.3)	
San Francisco	2,675 (6.8)	842 (4.9)	
Seattle	795 (2.0)	373 (2.2)	

Abbreviations. SD, standard deviation.—¹CD4 counts missing on 20,867 (52.9%) exposed subjects and 7,115 (41.0%) unexposed subjects.

TABLE II - NHL INCIDENCE IN 56,808 PERSONS WITH AIDS

Characteristic	NHL cases, <i>n</i>	Incidence, per 1,000 person-years	<i>p</i> -value
SV40 exposure status			0.06
Exposed	616	11.7	
Unexposed	230	10.1	
Sex and HIV risk group			<0.0001
Male homosexual	615	14.4	
Other male	146	8.4	
Female	85	5.7	
Ethnic group			<0.0001
White	496	15.0	
Black	142	5.7	
Hispanic	198	12.1	
Other/unknown	10	11.4	
Age at AIDS onset			0.09*
15-20	1	10.7	
21-23	11	7.9	
24-26	75	10.2	
27-29	198	10.2	
30-32	270	12.4	
33-35	251	11.7	
36-38	40	10.6	
Calendar year of AIDS onset			0.93*
1980-84	2	10.2	
1985-87	29	12.4	
1988-90	115	9.3	
1991-93	409	12.5	
1994-96	291	10.5	
CD4 count, cells/mm ³			<0.0001*
100+	111	6.7	
50-99	71	11.6	
0-49	244	14.9	
Registry			<0.0001
Atlanta	23	5.6	
Connecticut	24	10.0	
Florida	163	10.7	
Illinois	22	4.8	
Los Angeles	140	15.2	
Massachusetts	54	14.8	
New Jersey	83	9.0	
New York	161	9.0	
San Diego	52	22.5	
San Francisco	92	19.0	
Seattle	32	19.0	

**p*-value for linear trend.

incidence was 11.7 per 1,000 person-years in SV40-exposed subjects and 10.1 per 1,000 person-years in SV40-unexposed subjects (unadjusted relative risk 1.15, 95% CI 0.99-1.34, *p* = 0.06). As shown in Table II, NHL incidence varied across demographic categories. NHL incidence was elevated in males (12.6 per 1,000 person-years), especially in homosexual males (14.4 per 1,000 person-years), and in whites (15.0 per 1,000 person-years). NHL incidence increased steeply with declining CD4 counts at AIDS onset (*p* < 0.0001). NHL incidence tended to increase with age (*p* = 0.09), but there was no change with calendar time (*p* = 0.93). Substantial variation in NHL incidence across registry was also observed (Table II).

Because SV40-exposed and -unexposed cohorts differed in composition with respect to demographic factors that were themselves associated with NHL incidence (Tables I and II), we used Poisson regression to estimate the independent effect of SV40 exposure on NHL incidence. In a multivariate model (Table III), sex/HIV risk group, ethnic group and registry each remained highly significant predictors of NHL incidence, but there was no association between SV40 exposure and NHL (adjusted relative risk 0.97, 95% CI 0.79-1.20, *p* = 0.80). In a separate analysis restricted to subjects with CD4 counts, additional adjustment for this variable further reduced the relative risk associated with SV40 exposure (adjusted relative risk 0.74, 95% CI 0.52-1.07).

TABLE III - MULTIVARIATE REGRESSION ANALYSIS OF NHL RISK FACTORS

Characteristic	Relative risk (95% CI)	<i>p</i> -value
SV40-exposed	0.97 (0.79-1.20)	0.80
Sex and HIV risk group		<0.0001
Male homosexual	1.00	
Other male	0.71 (0.58-0.86)	
Female	0.51 (0.40-0.65)	
Ethnic group		<0.0001
White	1.00	
Black	0.51 (0.42-0.63)	
Hispanic	0.92 (0.78-1.10)	
Other/unknown	0.69 (0.37-1.29)	
Age at AIDS onset, years		0.73
15-20	1.07 (0.15-7.69)	
21-23	0.71 (0.38-1.33)	
24-26	0.86 (0.64-1.15)	
27-29	0.84 (0.68-1.03)	
30-32	1.00	
33-35	0.98 (0.83-1.17)	
36-38	0.93 (0.66-1.30)	
Registry		<0.0001
Atlanta	0.60 (0.39-0.94)	
Connecticut	1.13 (0.74-1.74)	
Florida	1.09 (0.87-1.37)	
Illinois	0.49 (0.31-0.77)	
Los Angeles	1.29 (1.02-1.63)	
Massachusetts	1.45 (1.06-1.98)	
New Jersey	1.13 (0.86-1.48)	
New York	1.00	
San Diego	1.77 (1.28-2.45)	
San Francisco	1.49 (1.14-1.95)	
Seattle	1.47 (0.99-2.16)	

We examined the association between SV40 exposure and NHL incidence within different ethnic groups. In these analyses stratified by ethnicity, the relative risk associated with SV40 exposure (adjusted for sex/HIV risk group, age and registry) was 0.89 (95% CI 0.68-1.17) among whites, 1.38 (0.82-2.31) among blacks and 0.88 (0.56-1.37) among Hispanics.

In addition, we examined the relation between SV40 exposure and the incidence of various NHL subtypes by site and histology (Table IV). Nodal NHL was associated with SV40 exposure in an unadjusted analysis (relative risk 1.46, 95% CI 1.14-1.86) but not after adjustment for demographic factors (adjusted relative risk 1.19, 95% CI 0.85-1.66). Central nervous system NHL and NHL of other/unknown site were not associated with SV40 exposure in either unadjusted or adjusted analyses. By histology, too few NHLs were classified as low grade, Burkitt's or "other" high grade to provide stable estimates of relative risk (Table IV). Nonetheless, no histologic subtype was significantly associated with SV40 exposure in either unadjusted or adjusted analyses.

DISCUSSION

In our cohort study of persons with AIDS, we did not find evidence that SV40 exposure was associated with an increased risk for NHL. Crude NHL incidence was slightly higher in SV40-exposed subjects (relative risk 1.15, 95% CI 0.99-1.34). However, the SV40-exposed and -unexposed cohorts differed in demographic composition. Along these lines, the AIDS epidemic in the U.S. can be viewed as a complex of mini-epidemics, arising at different times in different sex, ethnic and HIV-risk groups. During the early years of the epidemic, AIDS cases were predominantly among white homosexual men, whereas as the epidemic progressed, an increasing proportion of cases were in ethnic minorities and women.²⁴ Early AIDS cases made up a larger proportion of the SV40-exposed cohort than of the unexposed cohort (e.g., 22.1% vs. 10.4% of AIDS cases were from 1980-90; Table I). Accordingly, the exposed cohort had a larger proportion of males and whites. SV40-exposed individuals were also, on aver-

TABLE IV—NHL SUBTYPE-SPECIFIC INCIDENCE, BY EXPOSURE TO SV40-CONTAMINATED POLIOVIRUS VACCINE

NHL subtype	Cases, <i>n</i>	Incidence in SV40-exposed cohort, per 1,000 person-years	Incidence in SV40-unexposed cohort, per 1,000 person-years	SV40-associated relative risk, unadjusted (95% CI)	SV40-associated relative risk, adjusted (95% CI) ¹
Site					
Lymph node	364	5.34	3.66	1.46 (1.14–1.86)	1.19 (0.85–1.66)
Central nervous system	277	3.65	3.75	0.97 (0.75–1.26)	0.96 (0.67–1.37)
Other/unknown	205	2.72	2.74	0.99 (0.74–1.34)	0.73 (0.47–1.11)
Histology					
Low grade	4	0.08	0	— ²	— ²
Intermediate grade	219	3.04	2.60	1.17 (0.87–1.57)	0.94 (0.62–1.43)
High grade					
Burkitt's	19	0.25	0.26	0.93 (0.35–2.45)	— ²
Large cell, immunoblastic	113	1.65	1.15	1.44 (0.93–2.23)	1.06 (0.59–1.89)
Other high grade	27	0.34	0.40	0.86 (0.39–1.92)	— ²
Other/unknown	464	6.35	5.74	1.11 (0.90–1.35)	0.98 (0.74–1.30)

¹Adjusted for sex/HIV risk group, ethnic group, age, and registry. —²Relative risk not estimable (regression model did not converge).

age, 4.8 years older at AIDS onset than unexposed individuals. These factors (male sex, white ethnicity, older age) were each themselves associated with increased NHL incidence (Table II). After adjusting for the varying composition of the cohorts, SV40 exposure was no longer associated with NHL incidence (adjusted relative risk 0.97, 95% CI 0.79–1.20).

Three further analyses strengthened our conclusion that SV40 exposure was not linked to NHL. First, we did not see an association between SV40 exposure and NHL for any specific ethnic group. In the 1950s, fewer nonwhite than white children received the complete poliovirus vaccination series.²⁵ Nonetheless, even among whites with AIDS, NHL incidence was not increased in persons born in 1958–61. Second, SV40 was not associated with increased risk for particular NHL subtypes, including intermediate- and high-grade AIDS-associated NHLs, in which SV40 DNA was reported to be detected.⁴ Third, in additional analyses in which we slightly varied the birth years used to assign SV40 exposure and nonexposure, the relative risks of NHL associated with SV40 exposure were consistently close to unity (data not shown).

The lack of a significant association between SV40 exposure and NHL risk was not likely due to inadequacies in our registry linkage or insufficient numbers of subjects. The etiology of NHL in HIV/AIDS is unknown but is probably multifactorial. In our study, we were able to clearly identify established associations between NHL and demographic factors such as race and HIV risk group (Tables II and III, and as reported elsewhere²⁶). Immunosuppression plays a key role,²⁷ as demonstrated in our study by the strong relation between NHL incidence and CD4 count at AIDS. In at least some NHL cases, additional viral cofactors, such as Epstein-Barr virus and Kaposi's sarcoma-associated herpesvirus, are also important.^{1–3}

Our study used birth year to identify childhood exposure to SV40-contaminated poliovirus vaccine and thus to assign overall SV40 exposure status. To the extent that this assignment did not fully capture SV40 exposure, our results would have been biased towards a null finding. Nonetheless, 2 lines of evidence support the validity of our exposure assignment. First, there is good evidence that a large proportion of people born in 1958–61 received poliovirus vaccines containing live SV40. By late 1961, 87% of all U.S. children age 1–4 years had received at least 1 dose of poliovirus vaccine: 4% had received 1 dose, 9% had received 2 doses, 32% had received 3 doses and 42% had received 4 or more doses.²⁸ Based on this distribution of the number of doses received and an estimate that 10–30% of these doses contained live SV40,¹⁹ we calculate that 25–59% of persons born in 1958–61 were exposed at least once to live SV40 (*i.e.*, a weighted average of the probability of exposure given 1, 2, 3 or 4 doses; detailed calculations available on request). These SV40 exposures via contaminated vaccine resulted from direct injection with live virus and occurred early in life. This type of exposure closely mirrors the hamster

model, where inoculation with SV40 in the weaning period is potent in inducing lymphoma.¹⁰

Second, we would argue that people born in 1964–67 were not exposed to live SV40. Vaccines produced after 1962 were produced and tested in a manner that excluded SV40 contamination,^{29,30} so vaccination would not represent a potential route of SV40 infection.¹⁹ Human-to-human transmission of SV40 could conceivably occur, but no epidemiologic study has documented whether SV40 presently infects humans or is spread among asymptomatic persons. Routes of transmission for polyomaviruses, such as BK and JC viruses in humans and SV40 in macaques, are not well established. BK and JC are excreted in human urine.³¹ By comparison, data on the prevalence of SV40 in human urine are conflicting,^{31,32} but SV40 is not found in European and South African sewage,³³ suggesting that it is not a common human infection.

It is difficult to reconcile the results of recent laboratory studies with these negative epidemiologic data. Specifically, Vilchez *et al.*⁴ and Shivapurkar *et al.*⁵ reported that SV40 DNA sequences were detected in roughly 40% of NHLs, including 33–46% of AIDS-associated NHLs. In those studies, both laboratories relied on a high number of polymerase chain reaction (PCR) cycles to amplify SV40 sequences from archived tissues. Neither study quantified the amount of viral DNA detected, and SV40 could have been present in a very small amount (*i.e.*, <1 copy per tumor cell), mitigating against a biologic role.^{17,34} An additional unexplained finding in one study was the reported detection of SV40 in 5–10% of lung, breast, colon and prostate carcinomas.⁵ Both studies identified SV40 sequences in NHLs from individuals born after 1963,^{4,5} yet it is unclear how these people might have acquired SV40 infection. Interestingly, 2 additional PCR-based studies failed to find conclusive evidence of SV40 in NHLs,^{35,36} although the authors of one study did report detection of SV40 in concurrently evaluated mesotheliomas.³⁵ These types of inconsistencies have been seen in PCR-based studies of SV40 in other malignancies,⁶ including mesothelioma and brain tumors, whereas blinded evaluations of these tumors have not confirmed the presence of SV40.^{16,17} Finally, arguing further against a role for SV40 in NHL, a recent case-control study in Spain failed to detect an increased prevalence of SV40-reactive antibodies in NHL patients compared to controls.³⁷

In conclusion, our follow-up of more than 56,000 individuals with AIDS did not find increased risk for NHL among those exposed to SV40 through childhood vaccination, arguing against a causal role for SV40 in this malignancy. Additional follow-up studies of cohorts exposed to SV40-contaminated vaccines, including individuals not immunosuppressed by the effects of HIV, will be valuable. Further laboratory investigations of NHL patients, using rigorous and transparent protocols,¹⁶ are also needed.

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